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Long-Term Results of Therapy for Stage C Neuroblastoma

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Background: The appropriate therapy for Stage C neuroblastoma (NB) is uncertain. Because of the need for information applicable to the development of new randomized trials, we deemed it appropriate to investigate the patient characteristics, survival, patterns of failure, and complications of therapy in these children.
Methods: Search of the medical records of Duke University Medical Center from 1/1/60 to 3/1/95 disclosed 146 patients with NB, which included 13 Stage C patients.
Results: Mean age at diagnosis was 3.6 years. Twelve patients had primary abdominal tumors (92%) and one had a thoracic primary (8%). Twelve (92%) of the patients received chemotherapy including cyclophosphamide, 11 (85%), Adriamycin, 6 (46%), cisplatinum, 4 (30%), and VP 16, 4 (30%). All patients received radiotherapy (RT, mean dose administered 22.6 ± 8 Gy). With a mean follow-up of 8 years, the 10-year overall survival was 54% and the relapse-free survival was 46%. Four patients relapsed in the primary operative tumor bed and primary RT field, two relapsed in mediastinal or left supraclavicular lymph nodes as well as distantly following treatment of upper abdominal primaries, and in one the site of relapse is unknown. Long-term complications of therapy included two children who developed secondary malignancies associated with RT, two girls who developed primary ovarian failure, five children with clinically significant kyphosis and scoliosis, and one who suffered postoperative wound dehiscence following RT.
Conclusions: Although this study did not include modern techniques of staging with n-myc amplification and DNA index, the occurrence of next echelon nodal failures gives credence to the continuation of the dialogue concerning the appropriate role of "prophylactic" irradiation to mediastinal and left supraclavicular nodes in locally advanced upper abdominal NB. Documentation of significant long-term ill effects reinforces the need to critically evaluate the indications for RT.

KEY WORDS: **neuroblastoma, pediatric neoplasms, radiation therapy**

INTRODUCTION

Pediatric Oncology Group (POG) Stage C neuroblastoma (NB) is defined as disease with complete or incomplete resection of the primary tumor with positive intracavitary lymph nodes not adherent to the tumor [1–2]. Stage C constitutes ~ 10–15% of all cases of NB [1]. The prognosis for children with Stage C disease has been intermediate between that of resectable, lymph node negative NB, and the more common presentation of disseminated disease [1,3–10]. The therapy of Stage C remains

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contested. An upcoming randomized prospective POG trial is planned for n-myc = 1, Stage C NB in children > 1 year of age.

In view of the controversy concerning therapy in Stage C NB, it seemed appropriate to review critically the management of all children with this entity seen at our institution in the past 35 years. An analysis was conducted of the patterns of failure. Particular attention was paid to the late effects of therapy in long-term survivors.

MATERIALS AND METHODS

The initial patient population consisted of 146 children with NB seen at Duke University Medical Center between January 1, 1960, and March 1, 1995. Thirteen of these children (9%) had POG Stage C disease treated with surgery, radiotherapy, and/or chemotherapy, and comprise the study group. A retrospective chart review of these 13 patients was undertaken, with each evaluated for stage, age, gender, site of primary tumor, type of treatment, site(s) of recurrence, salvage regimens, salvage results, and complications of therapy. Incomplete records were updated with letters and telephone contacts.

Local failures (LF) were defined as tumor recurrence at the initial site of disease. Next echelon nodal failures were defined as tumor recurrence in lymph nodes continguous, but not immediately adjacent to, the primary tumor, i.e. mediastinal or supraclavicular nodes for an upper abdominal primary tumor. Distant failures (DF) were scored if disease recurred outside the above noted regions. Patients were classified by the International (INSS), Evans and D'Angio (ED), and Pediatric Oncology Group (POG) staging systems (Table I) [1,2,11,12]. Statistical analyses were conducted using the Kaplan-Meier method of survival calculation [13] with the Cox-Mantel test to compare survival distributions [14] as well as Student's t-test [15].

RESULTS

Patient Profile

The 13 individuals included 9 boys and 4 girls (ratio 2.25:1), eight Caucasians (69%), three African-Americans (23%), and 1 Asian-American (8%). Mean age at diagnosis was 3.6 years (range: 2 days, 19 years, 10 months). Three patients (23%) were <12 months of age at diagnosis and 10 (77%) were ≥ 1 year old.

Although the patients were, by definition, POG Stage C, by ED staging, 11 patients were Stage III (85%) and 2 were Stage 2B (15%). By INSS staging, 11 patients were Stage 3 (85%) and 2 were Stage 2B (15%).

Primary sites of disease included 12 abdominal (92%) and one thoracic (8%) presentation. Surgery consisted of biopsy only in 7 (54%), resection with microscopic positive margins in five (38%), and total resection in one (8%). Twelve of the patients received chemotherapy. The most commonly employed agents were cyclophosphamide, 11 (85%), Adriamycin, 6(46%), cisplatinum, 4(30%), and etoposide, 4(30%).

All patients were irradiated: eight with linear accelerators of either 4, 6, or 15 MV, (62%), two with cobalt 60 (15%), two with cesium 137 (15%), and one with 280 KV (8%). Eleven were irradiated once per day (85%), and two b.i.d. (15%). The mean radiation therapy (RT) dose was 22.6 ± 8 Gy. RT was only directed to the primary tumor bed without "prophylactic" irradiation of contiguous lymph nodes.

N-myc was measured in one patient and was not amplified.

Patterns of Failure

Four patients relapsed in the primary operative tumor bed/primary radiation field (mean dose 22 ± 8 Gy, not significantly different from those who did not relapse infield, 26 ± 5 Gy). Two children relapsed in mediastinal or left supraclavicular lymph nodes as well as distantly, following treatment of upper abdominal primaries, and in one the site of relapse is unknown. Thus local failure was a component of failure in 4/7 relapses (57%) and 4/13 patients (31%). Relapses occurred in children whose surgical treatment included biopsy only (4/7), resection with microscopic positive margins (2/5), and following gross total resection (1/1). There was no significant difference in age at diagnosis for those children who relapsed as opposed to those who did not. The one patient in whom n-myc was measured and was not amplified, relapsed locally.

Survival

With a mean follow-up of 8 years, the 10-year overall survival of the 13 patients was 54% with a relapse-free survival of 46% (Fig. 1). Two of the seven surviving patients were < 365 days of age at diagnosis. Thus two out of three of the patients < 365 days of age at diagnosis are alive without evidence of NB, whereas 5 of 10 patients ≥ 365 days of age at diagnosis are alive, albeit one of them with persistent disease.

Late Effects

Spinal complications. Five of the 7 surviving patients have spinal growth abnormalities partially attributable to RT. The 5 patients with kyphosis and/or scoliosis were irradiated at 4 months, 10 months, 12 months, 19 months, and 6 years, 4 months of age (mean 2.2 ± 2.4 years), with 20.35 to 25.5 Gy (Mean 24.25 ± 2 Gy) and followed for 4 years 9 months, 18 years 3 months, 22 years, 22 years, 4 months, and 23 years, 10 months from diagnosis (mean 18.2 ± 7 years). The two patients without axial skeletal abnormalities were irradiated at 4 years 7 months and 20 years 9 months of age (mean 12.6 ± 8 years) with 30 and 30.6 Gy (mean 30.3 ± 0.3 Gy) and

TABLE I. Neuroblastoma staging systems[a]

Evans & D'Angio(1,11)	Pediatric oncology group(1,12)	International staging system(1,2)
Stage I Tumor confined to the organ or structure of origin. Stage II Tumor extending in continuity beyond the organ or structure of origin but not crossing the midline. Regional lymph nodes on the ipsilateral side may be involved. Stage III Tumor extending in continuity beyond the midline. Regional lymph nodes may be involved bilaterally. Stage IV Remote disease involving the skeleton, bone marrow, soft tissue, and distant lymph node groups, etc. (see stage IV-S) Stage IV-S Patients who would otherwise be stage I or II, but who have remote disease confined to liver, skin, or bone marrow (without radiographic evidence of bone metastases on complete skeletal survey).	Stage A Complete gross resection of primary tumor, with or without microscopic residual. Intercavitary lymph nodes, not adhered to and removed with primary (nodes adhered to or within tumor resection may be positive for tumor without upstaging patient to stage C), histologically free of tumor. If primary in abdomen or pelvis, liver histologically free of tumor. Stage B Grossly unresected primary tumor. Nodes and liver same as stage A. Stage C Complete or incomplete resection of primary. Intercavitary nodes not adhered to primary histologically positive for tumor. Liver as in Stage A. Stage D Any dissemination of disease beyond intracavitary nodes, i.e., extracavitary nodes, liver, skin, bone marrow, bone. Stage DS Infants < 1 year of age with stage IV-S disease (see Evans and D'Angio column 1)	Stage 1 Localized tumor with complete gross excision, without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive). Stage 2A Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically. Stage 2B Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically. Stage 3 Unresectable unilateral tumor infiltrating across the midline,[b] with or without regional lymph unilateral tumor with contralateral regional lymph node involvement; or midline tumor wth bilateral regional lymph node involvement. Stage 4[c] Dissemination of tumor to distant lymph nodes, bone, bone marrow, liver, and/or other organs (except as defined in fS). Stage 4S Localized primary tumor as defined for Stage 1 or 2 with dissemination limited to liver, skin.[c]

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[a]Multifocal primary tumors (i.e. bilateral adrenal primary tumors) should be staged according to the greatest extent of disease, as defined above, and followed by a subscript letter M (i.e. 3_M).

[b]The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.

[c]Marrow involvement in stage 4S should be minimal; that is, <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensvie marrow involvement would be considered to be stage 4. The MIBG scan (if performed) should be negative in the marrow.

followed for 1 year 11 months and 7 years 7 months from diagnosis (mean 4.7 ± 2.8 years).

Three of the five patients with spinal growth abnormalities had relatively mild injuries: a right concave thoraco lumbar scoliosis in a patient treated for a dumbbell tumor without laminectomy, a right concave scoliosis in a patient irradiated for right abdominal tumor, and a 10° Cobb angle lumbar scoliosis in a child who has not yet reached puberty. Two patients had more severe injuries: a 79° thoracic kyphosis requiring resection and a stabilization rod in a child with a thoracic primary and a right thoracic (6°) left lumbar (5°) scoliosis treated with bracing in a child with abdominal primary tumor.

Ovarian Failure

Two of the 4 female long-term survivors suffered primary ovarian failure. Both received large field abdominal RT (20.35 and 24.75 Gy) at a young age (4 months and 1 year 7 months). One received 1 year of oral cyclophosphamide and the other received no chemotherapy. The diagnoses of ovarian failure were made at 15 and 16 years of age. Of the two female patients who did not have

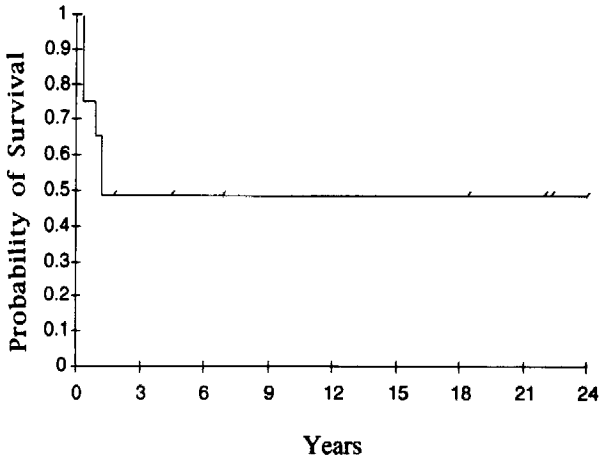

Fig. 1. The overall survival probability for 13 patients with Stage C neuroblastoma treated at Duke University Medical Center between 1960 and 1995 with surgery, radiotherapy, and, in all but one case, chemotherapy.

ovarian injury, one was diagnosed at 9 months of age and had thoracic RT and oral cyclophosphamide. The other child received abdominal RT plus cyclophosphamide and Adriamycin at 5 years 6 months of age but has not yet undergone puberty.

Second Malignant Neoplasms

Two of the three patients followed for > 20 years (67%) developed second malignant neoplasms. One patient was treated with a thoracotomy for a right paravertebral NB, 45 Gy at 3 Gy per fraction at maximum depth dose with a Cesium 137 unit to a posterior thoracic field (25.9 Gy at tumor depth), and 1 year of oral cyclophosphamide. Twenty-three years and 1 month following RT, she was diagnosed with a parascapular region dermatofibrosarcoma, which, as best as can be reconstructed, was at the edge or just beyond the edge of the RT field. The second patient underwent biopsy of a right adrenal NB, 20.35 Gy of local irradiation with anterior and posterior fields from a 6 MV linear accelerator, and oral cyclophosphamide. She developed a right retroperitoneal undifferentiated sarcoma in the middle of the irradiated region 21 years and 6 months after diagnosis and died with unresectable tumor.

DISCUSSION

Survival

Kushner et al. [16] have suggested that some cases of moderate to advanced NB can be treated with surgery alone. In 20 patients with INSS 2A to 4 disease and without unfavorable biologic features, an initial complete resection was achieved in seven. Only one of 20 patients received chemotherapy and all 20 are alive with a median follow-up of 32 months after diagnosis [16]. It is likely that some highly selected Stage C patients will be cured with surgery alone [17].

Wittenborg described the beneficial effect of postoperative irradiation in gross residual NB remaining after surgery [18]. Perez et al. [19] in 1967, reported a 41% (9/22) 5-year survival in children treated with limited surgical resection and postoperative irradiation. Only one of his 22 patients received adjuvant chemotherapy [19]. The sentinel historical series is the report of 1967 by Lingley et al. [20], which described local control achieved in 13 of 13 children with regional disease (in retrospect, Evans-D'Angio Stages II and III and POG Stages B and C) following incomplete resection and RT. Eight of the 13 patients were long-term survivors [20]. Lingley's report [20] was followed in 1971 by the report by Koop and Johnson [21] in which four of six irradiated patients with Evans-D'Angio Stage III NB survived their disease compared with one of seven children treated with surgery alone. Several recent studies have addressed the role of RT in either Evans-D'Angio Stage III or POG Stage C disease. The Italian Cooperative Group of Neuroblastoma randomized children > 1 year of age with minimal residual tumor following surgery or with lymph node involvement to receive 20 to 30 Gy of RT vs. no RT. All the patients received Peptichemio (a mixture of 6 oligopeptides of *m-L*-phenylalanine mustard thought to act by both alkylating and antimetabolic mechanisms). The relapse-free survival was the same between the two treatment groups [10].

In contrast to the Italian study, the prospective randomized POG Trial 8104 included patients older than 1 but < 21 years of age with Stage C NB. In this trial, patients were randomized to receive cyclophosphamide and Adriamycin following surgery vs. these drugs plus local RT. Second-look surgery was performed. Patients achieving a complete response then received cyclophosphamide and Adriamycin + cisplatinum and teniposide (VM 26). Those children failing to achieve a complete response received cisplatinum and VM 26 alone. Fifty-seven patients were evaluated. By Evans-D'Angio staging, the vast majority were Stage III and a few were Stage II. The complete response rate was better in the irradiated patients (76% vs. 46%, $P = 0.013$) as was the overall survival (73% vs. 41%, $P = 0.008$). This study was, of course, conducted prior to more detailed biologic markers being available [7].

Strother et al. [9] reported the preliminary results of POG Protocol 8742 for children > 12 months with Stage C NB. Patients, following initial surgery, received 5 courses of chemotherapy consisting of cisplatinum and etoposide alternating with cyclophosphamide and Adriamycin. Patients in complete remission after second-look surgery received further cyclophosphamide and Adriamycin + cisplatinum and etoposide, all others received involved field RT plus this drug combination. With

54 evaluable patients and relatively short follow-up, the overall survival rate is 71%. The most striking finding of this study involves the influence of n-myc amplification on outcome. The continuous rate of complete remission for those patients who had n-myc measured and had nonamplified tumors was 71% vs. 31% for patients with amplified n-myc. The survival probabilities were 79% (19 of 24) for patients with n-myc = 1 vs. 36% (4 of 11) for those with n-myc amplified tumors (9).

West et al. [8] reported a nonrandomized single arm trial from Boston Children's Hospital for children > 1 year of age at diagnosis with Evans-D'Angio Stage III NB. Twenty-five patients received surgery and MADDOCC (nitrogen mustard, doxorubicin, cisplatinum, DTIC, vincristine, cyclophosphamide) or cisplatinum/cyclophosphamide induction + MADDOCC. Sixteen of 25 children also received local RT. With a median follow-up of 7 years 1 month, the event-free survival was 72%. There were four local failures, but none were the sole site of failure. The one second malignant neoplasm, an osteosarcoma, was outside the RT field [8].

Late Effects

Spinal complications. Five of the seven surviving patients (71%) had kyphosis or scoliosis partially attributable to RT. Patients with spinal growth abnormalities were, on average, older and were followed for a longer period of time than those without abnormalities, although the patient numbers are too small for any meaningful test of statistical significance.

Makipernaa et al. [22] from Helsinki studied nine children with NB who were treated with RT (mean dose 28 Gy) who had survived for more than 11 years. Eight of the nine had scoliosis, six greater than 10°, and two had a curvature of 10°. Six of the nine had kyphosis. The most severe kyphosis was in a patient with a dumbbell tumor [22]. Mayfield et al. [23] reviewed the Children's Hospital Medical Center of Boston experience with 69 irradiated children with NB who had survived > 5 years. Sixty-seven of sixty-nine received orthovoltage RT. Fifty-six children had received RT and neither had a laminectomy, were paraplegic, or had tumor invasion of the axial skeleton. Of this group, 50% had post-RT scoliosis (5–79°) and 16% had kyphosis. Factors associated with spinal deformities in this series appeared to include orthovoltage RT, a dose >30 Gy, asymmetric irradiation of the spine, and epidural tumor spread [23].

One of our patients had a thoracic NB and was treated with surgery, chemotherapy, and RT. This long-term survivor had a 79° kyphosis and developed a second malignant neoplasm. The prognosis of localized thoracic NB, including dumbbell tumors, appears to be excellent [24–26]. It has been suggested by some investigators that many patients may be cured with surgery and chemotherapy only. This might avoid some ill effects associated with RT. For dumbbell tumors, significant long-term ill effects are associated with laminectomy. As many of these patients will be chemoresponsive, it may be possible to avoid aggressive surgery.

Our patients with spinal deformity confirm the observation that kyphosis and scoliosis are common in long-term survivors of NB who receive doses on the order of 20–30 Gy, even with megavoltage. Although asymmetric radiation of a growth plate, laminectomy, and/or a dumbbell tumor can result in more severe deformity, injuries can occur in the absence of such factors [18].

Ovarian failure. Primary ovarian failure requiring hormonal replacement occurred in both female patients receiving abdominal RT who had reached puberty. Normal ovarian function is required for normal growth, sexual development, and fertility. The ovary is particularly sensitive to RT and alkylating agent chemotherapy. There is an age-dependent response of the ovary to radiation dose with younger females being more resistant than older females. Nonetheless, doses >20 Gy are almost always sterilizing [27]. Both of our patients with primary ovarian failure received <20 Gy to large abdominal/upper pelvic fields.

Second malignant neoplasms. Two of our long-term survivors developed second malignant neoplasms. One second malignant neoplasm was clearly within a previous RT field, and one was adjacent to a RT field.

The Children's Cancer Research Group in Oxford maintains a registry of all children diagnosed with cancer in Great Britain and reported to the National Cancer Registry. A listing of second malignant neoplasms is also kept. Exclusive of retinoblastoma almost five times the number of second neoplasms were observed vs. those expected in childhood cancer survivors. The cumulative risk of second malignant neoplasms by 25 years from a 3-year survival of a first tumor was 3.7 ± 0.8% [28].

The Late Effect Study Group has described 308 second malignant neoplasms following treatment of 292 first tumors in children diagnosed between 1934 and 1980. Of the first neoplasms, 10% were NB. Second malignant neoplasms in 28 NB patients include 11 bone and soft tissue sarcomas (39%), 7 thyroid cancers, 5 leukemias or lymphomas, and 5 other histologies. In the entire patient population, 68% of second malignant neoplasms develop in irradiated tissue [29].

Patterns of Failure

We identified some cases of next echelon nodal failure, but in no case was this without concurrent failure elsewhere. Among the patients reviewed by Matthay et al. [4], local failure and distant failure were noted regardless of the primary sites of disease (pelvis, abdomen, chest, and neck). In no case did nodal failure occur as an isolated

event [4]. Rosen et al. [5] described seven patients who failed, all having either thoracic or abdominal disease at diagnosis. Relapses were evenly distributed between local failure, distant failure, and combined sites. No specific information was given on lymph node recurrence [5]. Our data, combined with these other results, suggest that next echelon nodal failure is associated with failure elsewhere and is relatively frequent. An argument may be made to surgically sample and/or prophylactically irradiate the mediastinum and supraclavicular regions for upper abdominal POG Stage C disease. Arguing against this suggestion are the known risks of chest RT in a young child, the possible compromise of chemotherapy administration by large field RT, and the fact that next echelon nodal failure is unlikely to occur as an isolated event. With the prevalence of distant failure alone or as a component of overall failure, continued research into systemic therapy is critical.

CONCLUSIONS

Contemporary studies utilize DNA ploidy, n-myc amplification, the presence or absence of TRK, serum ferritin, and chromosomal abnormalities to predict prognosis of NB and direct therapy [2,11–12,30–36]. Our documentation of significant long-term ill effects of RT re-enforces the need to evaluate critically the indications for RT in Stage C. An upcoming POG randomized prospective trial will assess the role of RT in children >1 year of age with n-myc = 1 tumors treated with initial surgery and chemotherapy. Although our retrospective review did not include modern techniques of staging with n-myc amplification and DNA index, the occurrence of next echelon nodal failure gives credence to the continuation of the dialogue concerning the appropriate role of "prophylactic" irradiation to large fields, possibly including the mediastinum in locally advanced upper abdominal NB.

REFERENCES

1. Halperin EC, Constine LS, Tarbell NJ, Kun LE: "Pediatric Radiation Oncology," 2nd ed. New York: Raven Press, 1994, p 140–170.
2. Brodeur GM, Pritchard J, Berthold F, et al.: Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 11:1466–1477, 1993.
3. Nitschke R, Smith EI, Altshuler G, et al.: Postoperative treatment of nonmetastatic visible residual neuroblastoma: A Pediatric Oncology Group study. J Clin Oncol 9:1181–1188, 1991.
4. Matthay KK, Sather HN, Seeger RC, et al.: Excellent outcome of stage II neuroblastoma is independent of residual disease and radiation therapy. J Clin Oncol 7:236, 1989.
5. Rosen EM, Cassady JR, Frantz CN, et al.: Neuroblastoma: The Joint Center for Radiation Therapy/Dana-Farber Cancer Institute/Children's Hospital experience. J Clin Oncol 2:719, 1984.
6. Halperin EC, Cox EB. Radiation therapy in the management of neuroblastoma: The Duke University Medical Center experience 1967–1984. Int J Rad Onc Biol Phys 12:1829, 1986.
7. Castleberry RP, Kun LE, Altshuler G, et al.: Radiotherapy improves the outlook for patients older than one year with Pediatric Oncology Group stage C neuroblastoma. J Clin Oncol 9:789, 1991.
8. West D, Shamberger RC, Macklis RM, et al.: Stage III neuroblastoma over 1 year of age at diagnosis: Improved survival with intensive multimodality therapy including multiple alkylating agents. J Clin Oncol 11:84–90, 1993.
9. Strother D, Cantor A, Halperin E, et al.: Treatment of Pediatric Oncology Group (POG) stage C neuroblastoma (NBL): A preliminary POG report. Proc ASCO 12:415, 1993.
10. Garaventa A, DeBernardi B, Pianca C, et al.: Localized but unresectable neuroblastoma: treatment and outcome of 145 cases. J Clin Oncol 11:1770–1779, 1993.
11. Evans AE, D'Angio GJ, Propert K, et al.: Prognostic factors in neuroblastoma. Cancer 59:1853, 1987.
12. Castleberry RP, Shuster JJ, Altshuler G, et al.: Infants with neuroblastoma and regional lymph node metastases have a favorable outlook after limited postoperative chemotherapy: A Pediatric Oncology Group study. J Clin Oncol 10(8):1299, 1992.
13. Kaplan EL, Meier P: Non-parametric estimation from incomplete observations. J Am Stat Assoc 53:457, 1958.
14. Cox DR: Regression models and life tables. J R Stat Soc Ser B 34:187; 1972.
15. Norman GR, Streiner DL: Biostatistics: The bare essentials. St. Louis: Mosby, 1994, p 58–63.
16. Kushner BH, LaQuaglia MP, Cheung N-KV: Rethinking management of localized neuroblastoma. J Clin Oncol 11:1832–1833, 1993.
17. D'Angio GJ, Matthay KK, Evans AE: Role of radiotherapy in neuroblastoma. J Clin Oncol 9:2076, 1991.
18. Wittenborg MH. Roentgen therapy in neuroblastoma: A review of 73 cases. Radiology 54:679–688, 1950.
19. Perez CA, Vietti T, Ackerman LV, et al.: Tumors of the sympathetic nervous system in children: An appraisal of treatment and results. Radiology 88:750–760, 1967.
20. Lingley JF, Sagerman RH, Santulli TV, Wolff JA: Neuroblastoma: Management and survival. N Eng J Med 277:1227–1230, 1967.
21. Koop CE, Johnson DG. Neuroblastoma: An assessment of therapy in reference to staging. J Pediat Surg 6:595–600, 1971.
22. Makipernaa A, Heikkila JT, Merikanto J, et al.: Spinal deformity induced by radiotherapy for solid tumours in childhood: A long-term follow up study. Eur J Pediat 152:197–200, 1993.
23. Mayfield JK, Riseborough EJ, Jaffe N, Nehme AME: Spinal deformity in children treated for neuroblastoma. J Bone Joint Surg 63A:183–193, 1981.
24. Castel V, Badal MD, Bezanilla JL, et al.: Treatment of stage III neuroblastoma with emphasis on intensive induction chemotherapy: A report from the neuroblastoma group of the Spanish society of pediatric oncology. Med Pediat Oncol 24:29–35, 1995.
25. Plantaz D, Hartmann O, Kalifa C, et al.: Localized dumbbell neuroblastoma: A study of 25 cases treated between 1982 and 1987 using the same protocol. Med Pediat Oncol 21:249–253, 1993.
26. Rubie H, Hartmann O, Giron A, et al.: Nonmetastatic thoracic neuroblastomas: a review of 40 cases. Med Pediat Oncol 19:253–257, 1991.
27. Torano AE, Halperin EC, Leventhal BG: The ovary. In Schwartz CL, Hobbie WL, Constine LS, Ruccione KS (eds): "Survivors of Childhood Cancer: Assessment and Management." St. Louis: Mosby, 1994, p 213–214.
28. Hawkins MM: Second primary tumors following radiotherapy for childhood cancer. Int J Rad Oncol Biol Phys 19:1297–1301, 1990.
29. Meadows AT, Baum E, Fossati-Bellani F et al.: Second malignant neoplasms in children: an update from the Late Effects Study Group. J Clin Oncol 3:532–538, 1985.
30. Coldman AJ, Fryer JH, Elwood JM, Sonley MJ: Neuroblastoma: Influence of age at diagnosis, stage, tumor site, and sex on prognosis. Cancer 46:1896, 1980.
31. Hayes FA, Green A, Hustu HO, Kumar M: Surgicopathologic staging of neuroblastoma: Prognostic significance of regional lymph node metastases. J Pediat 102:59, 1983.
32. Ninane J, Pritchard J, Morris Jones PH, et al.: Stage II neuroblastoma. Adverse prognostic significance of lymph node involvement. Arch Dis Childhood 57:438, 1982.
33. Breslow N, McCann B: Statistical estimation of prognosis for children with neuroblastoma. Cancer Res 31:2098, 1971.
34. Shuster J, McWilliams NB, Castleberry R, et al.: Serum lactate dehydrogenase in childhood neuroblastoma: A Pediatric Oncology

Group recursive partitioning study. Amer J Clin Oncol 15(4): 295, 1992.
35. Joshi VV, Cantor AB, Altshuler G, et al.: Age-linked prognostic categorization based on a new histologic grading system of neuroblastomas. Cancer 69:2197–2211, 1992.
36. Bowman LC, Hancock ML, Santana VM, et al.: Impact of intensified therapy on clinical outcome in infants and children with neuroblastoma: The St. Jude Children's Research Hospital experience, 1962 to 1988. J Clin Oncol 9:1599–1608, 1991.